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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,343	04/07/1998	UFFE LOEVBORG	3556.224-US	5207

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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1652	24

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/056,343	Applicant(s) LOEVBORG, UFFE	
	Examiner William W. Moore	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 and 30 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-66 and 77-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-53,56-62,65,66,77-82,87-92,95 and 96* is/are rejected.

7)☒ Claim(s) *54, 55, 63, 64,83, 84, 93, and 94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendments

Applicant's Amendment E, Paper No. 23 filed October 30, 2002, has been entered, adding the new claims 77-96 and canceling the claims 67-76 that were previously entered with Amendment D, Paper No. 22 filed October 9, 2002. Claims 48-66 submitted with Applicant's earlier Amendment C, Paper No.17 filed on November 1, 2001, also remain in the application, thus claims 48-66 and 77-96 are pending herein. Applicant's Terminal Disclaimer, Paper No. 18 filed November 1, 2001, overcame the obviousness-type double patenting of record stated in Paper No. 15, mailed May 1, 2001.

Claim Rejections - 35 USC §§102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. §122(b). Therefore, this application is examined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-50, 56-59, 65 and 66 remain rejected, and claims 77-79, 85-89, 95 and 96 are rejected, for reasons of record under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Ladner et al., U.S. 5,223,409, made of record herewith.

Applicant's arguments filed October 9, 2002, have been fully considered with respect to the previously-rejected claims 48-50, 56-59, 65 and 66 and were also considered as they may apply to the new claims 77-79, 85-89, 95 and 96 rejected herein, but they are not persuasive. Applicant suggests that the disclosure of Ladner et al. of modification of the amino acid sequence of a polypeptide, the medicinally active enzyme streptokinase, that is "antigenic to an undesirable extent" to produce a variant polypeptide with reduced allergenicity is deficient because Ladner et al. (1) map antigenic epitopes generally during their screening procedure, rather than specifically, a priori, (2) do not explicitly state that that a resulting, epitope-reduced, streptokinase be functional, and, (3) do not require that the IgE response to the altered, epitope-reduced, enzyme be reduced to render it less allergenic in animals. In each instance, Applicant argues limitations absent from the claims.

(1) No claimed method requires any particular order of events where preambles of claims 48, 58, 77, and 87, each recite "comprising", permitting the following steps to be taken in any order, and even if limitations requiring a specific series of processes were introduced in claims 48, 58, 77, and 87, Ladner et al. would still remain available as prior art under 35 U.S.C. §103(a) where the processes of Ladner et al. comprise essentially the same procedures to produce the same result indicated in Applicant's claimed methods.

(2) No claimed method requires that a DNA molecule encode a variant that has the full, or even a partial, biological activity of the reference protein, only that the molecule encode a less antigenic variant and even if a limitation as to function were introduced in claims 48, 58, 77, and 87, Ladner et al. disclose, col. 103, lines 6-8, that "mutants are tested to verify that the [desired] properties have not been altered to an unacceptable degree by the mutations".

(3) The claims do not require that any particular kind of epitope region, such as IgE epitopes, be identified for modification any reference protein, e.g., to reduce allergenicity in a variant, only that a generic "lower immunogenic response" be invoked in animals exposed to the variant. Indeed the first step of the process that Ladner et al. disclose, preparing DNA segments encoding several "Initial Potential Binding Domains" [IPBDs] that are consecutive peptide regions of a polypeptide that are undesirably antigenic, permits the reduction of an immune system response caused by any kind of epitope, relative to the response to the unaltered, reference protein, in persons or animals exposed to the variant.

It is further noted that no recitation of a claimed method specifically excludes the piecemeal method of Ladner et al. wherein DNA segments specifying variegated epitope regions are comprised within multiple conveying DNA sequences, expression vectors, termed "Genetic Package[s]" [GP], permitting a host cell maintaining a GP to display each variegated PBD peptide on the surface of an expressed carrier molecule, a coat protein of a bacteriophage. While Ladner et al. do not use the term "epitope", the artisan reading their disclosure would recognize that the "antigenic determinants" which Ladner et al. discuss, i.e., the native IPBDs that bind most effectively in their method to a detecting antibody surface, are epitopes. Claims 87-89, 95 and 96 are included in this rejection because, even though a process using as series of monoclonal antibodies is preferred by Ladner et al. is preferred, the disclosure of Ladner et al. of a further steps of contacting both the several native, IPBDs and their corresponding, variegated, PBDs with a surface covered with antibodies raised in a subject to the polypeptide that is undesirably antigenic may be a contacting, col. 103, lines 9-30, with polyclonal antisera in a recursive process that includes a composite assessment of the binding affinity of each of the carrier molecule-displayed IPBDs, and the binding affinities of their corresponding variegated PBDs, to determine which peptide sequences of the variegated PBDs bind with reduced affinity to

the antibody-covered surface and selection of those sequences that bind with reduced affinity as replacements for the corresponding peptide region of the undesirably antigenic polypeptide. Ladner et al. then recapitulate the methods described by claims rejected here in their disclosure of the preparation of a DNA encoding the modified polypeptide, expressing it in a host cell to produce a modified, composite, polypeptide having reduced immunogenicity by comparison with the native undesirably immunogenic polypeptide, and capable of evoking a lower immunogenic response in an animal than the native undesirably antigenic polypeptide, and then testing it to ensure that it maintains its desired activity despite the amino acid sequence modification that incorporates a variegated peptide region replacing a native peptide region to produce a lower immunogenic response in an animal.

Ladner et al. are considered to have rendered both the methods of claims 48-50, 56-59, 65 and 66, as well as of the new claims 77-79, 85-89, 95 and 96, obvious to one of ordinary skill in the art at the time the invention was made because they teach each step needed to practice a method set forth in the claims, order the steps in a process that will provide results the claims describe, teach a medicinal polypeptide known to evoke an immunogenic response in animals that would be more efficacious were its immunogenicity lowered, thus providing motivation to do so, and also disclose many examples of practicing each step of the method taught in section "V.R." elsewhere in the patent, with other polypeptides and their encoding DNAs, thus providing a reasonable expectation of success in practicing their methods to an artisan at that time. So long as the claimed methods embrace a scope of subject matter coextensive with the disclosure of Ladner et al., this rejection of record will be maintained.

Claim Rejections - 35 USC §103

Claims 51-53, 60-62, 80-82, and 90-92 are rejected for reasons of record under 35 U.S.C. §103(a) as obvious over Ladner et al., U.S. 5,223,409, as applied to claims 48-50, 56-59, 65 and 66 above, in view of either Zacharaiae et al., 1981, Allergy, Vol. 36, pages 513-516, or Arlian et al., 1990, International Archives of Allergy and Applied Immunology, Vol. 91, pages 278-284, both of record.

Applicant's arguments filed October 9, 2002, have been fully considered with respect to the previously-rejected claims 51-53, 60-62, and were also considered as they may apply to the new claims 80-82, and 90-92 rejected herein, but they are not persuasive. Applicant suggests in Paper No. 23 that the absence of a teaching of a specific DNA sequence in either of Zacharaiae et al. or Arian et al., renders them inapplicable as prior art, but, as noted in Paper No. 21 mailed April 9, 2002, the claims require no particular amino acid sequence for a reference protein, do not require that a particular epitope region be altered in any reference protein, require no particular amino acid sequence modification to reduce allergenicity and amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Zacharaiae et al. to cause IgE antibody-mediated sensitization in persons, resulting in chronic, symptoms of respiratory irritation, coughing, shortness of breath, and chest tightening serine proteases and the amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Arlian et al. to cause respiratory allergy and to exhibit specific, electropositive antigens binding significant levels of human IgE antibodies as demonstrated by crossed immunoelectrophoresis, were already know in the art at the time the invention was made. Thus one of ordinary skill in the art at that time would have had ample motivation to design and synthetically produce generic DNA sequences encoding each protease to permit mutation and variegation of amino acid sequences of peptide regions identified as an antigenic determinants in a method of Ladner et al., and such an artisan would have had a reasonable expectation of success in preparing a variant of any or all of these enzymes that would evoke a lowered immunogenic response in a person where suitable IgE antibodies could be isolated from exposed individuals to conduct the screening steps of Ladner et al. that identify the significant antigenic determinants and permit measuring of reduced binding to antibody to identify variegated peptides that, when replacing the antigenic determinant, or epitope, in

a variant subtilisin will render the variant subtilisin capable of evoking a lowered immunogenic response in a person. The rejection of record is maintained.

Allowable Subject Matter

Claims 54, 55, 63, 64,84, 84, 93, and 94 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. While Gerber, U.S. 4,945,043, made of record herewith, discloses that an amylase - a process enzyme according to claims 54, 55, 63 and 64 - possesses epitopes, as measured by the response of one animal's immune defense system to exposure to a foreign amylase, nothing in Gerber, nor in the other prior art of record, suggests that "process" enzymes that are not also "industrial" enzymes cause sensitization or allergy in those handling them to any noticeable extent. While the prior art provides motivation for one of ordinary skill in the art, at the time the invention was made, to apply the method of Ladner et al. to a particular "process" enzyme which is an "industrial" enzyme, or to a class of "process" enzymes which are also "industrial" enzymes, such motivation cannot be extended to apply that method to enzymes that are particularly "process" enzymes and not "industrial" enzymes to produce variants having lower immunogenic potential than the native enzyme.

Conclusion

Applicant's amendment necessitated the application of previous ground(s) of rejection presented in this Office action to newly submitted claims. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is

703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct FAX telephone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
January 10, 2003

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